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PATENT



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Alan Gewirtz**

Confirmation No.: **6995**

Serial No.: **09/993,183**

Group Art Unit: **1635**

Filing Date: **November 14, 2001**

Examiner: **Kimberly Chong**

For: **Post-Transitional Gene Silencing by RNAi in Mammalian Cells**

Mail Stop Appeal Brief-Patents

Commissioner for Patents

P.O. Box 1450

Alexandria, VA 22313-1450

Dear Sir:

APPELLANT'S REPLY BRIEF PURSUANT TO 37 C.F.R. § 41.41

This brief is in reply to the Examiner's Answer, dated February 8, 2008. The Notice of Appeal was filed on July 2, 2007, and Appellant's Brief was filed November 2, 2007, both of which were timely.

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1. STATUS OF CLAIMS

Claims 1, 2, 5, 7-9, 11, and 21-38 are currently pending, and each stands finally rejected. The rejection of claims 1, 2, 5, 7-9, 11, and 21-38 is appealed.

2. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds of rejection to be reviewed on appeal are:

Whether claims 1, 2, 5, 7-9, 11, 21-22, and 24-27 are patentable under 35 U.S.C. § 102 (b) in view of Fire *et al.* (U.S. Patent No. 6,506,559) ("Fire").

Whether claims 1, 2, 5, 7-9, 11 and 21-38 are patentable under 35 U.S.C. § 103 (a) over Fire, Gewirtz *et al.*, WO 92/19252 ("Gewirtz"), and Sharp, *Genes & Dev.* 13:139-141, 1999.

3. ARGUMENT

Summary of Argument

The rejection of claims 1, 2, 5, 7-9, 11, 21-22, and 24-27 under 35 U.S.C. § 102 (b) should be reversed. The rejection is premised on an incorrect legal standard for determining whether the asserted Fire reference enables the practice of Appellant's claimed invention. This resulted in an erroneous determination of whether the Fire reference is an enabling reference with respect to Appellant's claimed invention because the factual predicate underlying the legal conclusion was improper.

The rejection of claims 1, 2, 5, 7-9, 11 and 21-38 under 35 U.S.C. § 103 (a) over Fire, Gewirtz, and Sharp should also be reversed. There was no motivation to combine the references, and, there was no reasonable expectation of success, given the state of the art. Further, the asserted references in combination do not disclose or suggest all the features of Appellant's claimed invention. The Examiner erred in giving no weight to the claimed feature "human cell." The Examiner erred in disregarding the teachings away in the references themselves, and in failing to consider each of the references and Appellant's claimed invention as a whole.

I. Reply to Rejection Under 35 U.S.C. § 102(b): The Claims are Novel Over Fire

Appellant respectfully maintains that the claims are novel over Fire and that the rejection should be reversed because Fire did not enable the practice of Appellant's invention at the time of Appellant's filing. Thus, Fire is not novelty-destroying under 35 U.S.C. § 102 (b), as briefed in Appellant's Brief Pursuant to 37 C.F.R. § 41.37 ("Appellant's Brief").

A. *Fire is not Anticipatory: It Did Not Enable Appellant's Claimed Invention*

Examiner's Answer asserted that although "Fire *et al.* did not reduce to practice his invention, that does not mean the invention is not enabled." Examiner's Answer, Section (10), page 9- 15. The Examiner's Answer alleges that Fire is an enabling reference because: (1) "thousands of post-filing art references have repeatedly shown that the methods of Fire *et al.* work in human cells;" (2) Appellant has allegedly not demonstrated any manipulative or structural differences between the claimed invention and Fire; and (3) Dr. Fire won a Nobel Prize related to his RNAi work. None of these allegations are evidence, nor are they probative of whether the Fire reference enables the practice of Appellant's claimed invention.

1. The Examiner's Reliance on Post-Filing date References is Improper

The Examiner erred in relying on unspecified "post-filing art" (see e.g., Examiner's Answer, page 10, lines 4-5; page 11, lines 2-3; page 13, lines 7-8; page 15, lines 12-13) to bolster her conclusion that Fire enabled Appellant's claimed invention. The use of post-filing date references is strictly circumscribed by the Federal Circuit. It is well-settled that later-dated publications cannot supplement an incomplete disclosure in a prior art reference to render it enabling. The Federal Circuit approved the use of later publications in certain circumstances "as evidence of the state of the art *existing on the filing date* of an application." See *Gould v. Quigg*, 822 F.2d 1074, Fed. Cir. (1987). Thus, except where the Examiner has entered specific post-filing references into evidence for this purpose, she is not entitled to rely upon any such art. Only two specific post-filing date references, Zamore and Kreutzer, have been cited in the Examiner's Answer. Neither Zamore nor Kreutzer support the contention for which they are cited.

Zamore (September 2001), cited at page 10, line 9 of the Examiner's Answer, published 10 months after Appellant's priority date. Zamore states that RNAi is an important tool in *C. elegans*, fruit flies and other insects, trypanosomes, planaria, and hydra. Zamore further states that the utility of RNAi as a "reverse genetic tool," or gene silencing tool, for somatic mammalian cells is severely limited by the sequence-nonspecific responses of mammals to long dsRNA. As with the other evidence of record, Zamore's list of organisms lacks *any* vertebrates.

Kreutzer (August 200)(see page 15, line 14) was cited as evidence that Fire's methods work in mammalian cells. Kreutzer has been antedated with respect to Appellant's claims. The Examiner is not entitled to rely on any results or teachings of Kreutzer, other than those regarding the state of the art *existing at the time of Appellant's filing*. All that Kreutzer provides as to the state of the art of RNAi existing at the time of Appellant's filing is the simple statement that "[n]othing is mentioned in [the Fire *et al.* Nature paper] on the activity of specific dsRNA with regard to inhibiting the gene expression, in particular in mammalian and human cells".

The Examiner's reliance on unspecified post-filing date references is improper in the determination of whether Fire enabled that practice of Appellant's claimed invention. Such reliance disregards the state of the art *existing at the time of Appellant's filing*. The Examiner's analysis reveals a failure to recognize that the state of the art was changing. The state of the art existing, for example, one year after Appellant's filing date, was not probative

of the state of the art *existing at the time of Appellant's filing*. What the person of ordinary skill knew, and what that person may have been enabled to do regarding RNAi, was different at those two time points. See e.g. the September 14, 2005 declaration of the inventor, Dr. Alan M. Gewirtz ("Gewirtz Declaration") (Exhibit 8, Appellant's Brief), paragraphs 14-24. Whether Fire was enabling requires analysis of the state of the art existing at the time of Appellant's filing, not at a later time. As the court in *Elan Pharm. Inc. v. Mayo Found. For Med. Educ. & Research*, 346 F.3d 1051, 1054, 68 USPQ2d 1373 (Fed. Cir. 2000) stated "an enablement determination is made retrospectively, i.e., by looking back to the filing date of the patent application and determining whether undue experimentation would have been required to make and use the claimed invention at that time" based on the allegedly anticipatory reference.

Reliance on post-filing date references (Examiner's "thousands" of references) also caused the Examiner to improperly discount evidence of record. For example, the Examiner dismissed as "mere speculation" the statements made by Dr. Fire in his 1999 Trends in Genetics paper ("Fire TIG") (Exhibit 1, Appellant's Brief) questioning the existence of RNAi in vertebrates, and stating that the protocols used for RNAi in invertebrate and plant systems are unlikely to be effective in vertebrates. See paragraph beginning on Examiner's Answer, page 10, line 15. The Examiner's sole basis for dismissing Dr. Fire's admission is that the statements were allegedly *later* proved unfounded, given the "voluminous amount of post-filing art that has shown the methods of Fire *et al.* work in humans." Such analysis again fails to consider the required *retrospective nature* of the enablement inquiry. The skilled artisan at the time would not have had the benefit of any post-filing date art, but instead would have read and evaluated Dr. Fire's statements in Fire TIG doubting the existence of RNAi in vertebrates and expressing doubt that invertebrate protocols would work in vertebrates.

Appellant's Brief summarized the evidence of record, which demonstrates that the skilled artisan would not have found Fire to be an enabling reference for the practice of RNAi in mammalian cells in the period leading to Appellant's filing date.

2. The Examiner's Reliance on "Manipulative Differences" in the Claims is Improper

The Examiner's reliance on whether or not there were "manipulative or structural differences" between the claims and the disclosure of Fire, is improper.

The Examiner's Answer states:

Further evidence that Fire *et al.* sufficiently described methods of mediating RNAi in human cells comes from Appellant's instantly claimed invention because there are not any manipulative differences or any structural differences in the steps used in the instantly disclosed methods as compared to the methods disclosed by Fire.

Examiner's Answer, page 15, lines 7-10 (See also page 10, lines 9-12; page 11, lines 9-11).

As a preliminary matter, a proper rejection for anticipation under 35 U.S.C. § 102, requires that each and every element in the claim be found, either expressly or inherently, in a single prior art reference. Therefore, by definition, there will be no manipulative or structural differences between the claimed subject matter and the prior art. However, even if the claimed invention is disclosed in the allegedly anticipatory reference, that disclosure will not suffice as prior art if it was not enabling. *In re Borst*, 345 F.2d 851,855, 145 USPQ 554, 557 (CCPA 1965) (*cert. denied*).

The presence or absence of manipulative or structural differences between Fire and Appellant's claimed invention is not germane to whether Fire enabled Appellant's claims. The Examiner's analysis is flawed because, if Fire's disclosure did not enable the practice of Appellant's claimed invention, then there need not be any "manipulative differences" between Fire and Appellant's claims. "It is insufficient to name or describe the desired subject matter, if it cannot be produced without undue experimentation". *Elan Pharm. Inc. v. Mayo Found. For Med. Educ. & Research*, 346 F.3d 1051, 1055, 68 USPQ2d 1373 (Fed. Cir. 2000)

3. Dr. Fire's Nobel Prize is Not Evidence of Whether the Fire Reference Enabled the Practice of Appellant's Claimed Invention

The Examiner's Answer alleged that Fire was enabling of Appellant's claims, in part because:

"[i]n fact, Fire *et al.* won a Nobel Prize for their discovery, largely based upon the implications of its use in humans. . ."

The Examiner is seeking to have the Board take judicial notice of the fact that Dr. Fire received a Nobel Prize. Appellant respectfully requests that the Board decline to do so, because the award of Dr. Fire's Nobel Prize is not probative of whether Fire was an enabling reference in the relevant time frame. Moreover, during his Nobel Lecture on December 8,

2006, Dr. Fire, stated that mammals were not generally amenable to RNAi at the time of Appellant's filing. Specifically he stated:

Soon after the initial description of dsRNA-triggered silencing in *C. elegans*, several descriptions of similar processes appeared for other groups of organisms. These initially included observations from *Drosophila* (a fruit fly), Trypanosomes (single cell parasites), and plant systems [55–58], with many other organisms rapidly joining the list. *Mammals were conspicuously absent from the initial list of organisms generally amenable to this type of manipulation. The exclusion of mammals from the list of easily manipulated species was not a surprise: the non-specific responses to dsRNA that were originally discovered by Hilleman and colleagues [14] were certainly sufficient to confound any analysis of specific genetic interference.* Nonetheless, early efforts in this area provided both an indication of the potential existence of specific dsRNA responses in certain specialized mammalian cell systems (e.g. oocyte and ovary cells [59–61]) and of the predominance of the non-specific response in most others [e.g. 62].

Dr. Fire's Nobel Prize acceptance speech in 2006, like the award of his Nobel Prize, is a matter of public record. His speech was retrospective in nature, and thus cannot be deemed to be "mere speculation" as to the state of the art at the relevant time. Dr. Fire summarized the state of the art from the time of publication of their early work (i.e. 1997) through research then current, i.e., 2006. Thus, Dr. Fire's receipt of the Nobel Prize, is not relevant to the questions of this appeal and, if anything, his Nobel Prize acceptance speech fully supports Appellant's argument.

4. The Examiner Has Misconstrued the Evidence of Record

The Examiner failed to weigh Appellant's evidence in terms of what a skilled artisan at the time of Appellant's filing would have understood or been able to practice without undue experimentation. This evidence was introduced to establish that Fire did not enable Appellant's claimed invention at the time of Appellant's filing.

For example, the Examiner misconstrued the impact of Fire's admission in Montgomery and Fire (*Trends in Genetics* 14(7):255-257 (1998) ("Montgomery and Fire") (Exhibit 2, Appellant's Brief)). The authors addressed likely problems to be faced in attempting RNAi in PKR-proficient mammalian cells. The Examiner's Answer alleged that (a) there were no manipulative differences between Appellant's methods and those of Fire, and (b) Appellant exemplified RNAi in mammalian cells using a long dsRNA exemplified by Fire to mediate RNAi in invertebrates. Examiner's Answer, page 11, lines 9-16.

Montgomery and Fire's statements of the problems associated with the PKR response were not offered by Appellant to distinguish his claims over Fire, but as evidence that Fire did not enable the skilled artisan at the time to practice Appellant's claimed invention.

Further, Appellant's use of a "long dsRNA" is evidence that, in fact, Appellant proceeded in the face of established wisdom that taught long dsRNA were specifically targeted by the PKR system in mammalian cells. See, e.g., page 5, paragraph 10 of the Gewirtz Declaration. See also Zamore, discussed at Section I.B.1, *supra*.

Similarly, the Examiner's treatment of Appellant's evidence from Paddison *et al.* ("Paddison") (Exhibit 5, Appellant's Brief), Wianny *et al.* ("Wianny") (Exhibit 6, Appellant's Brief), and Svoboda *et al.* ("Svoboda") (Exhibit 7, Appellant's Brief) is incorrect. These references provide evidence of the state of the art of RNAi in mammalian cells at the time of Appellant's filing.

The Examiner first alleges that the evidence is not convincing because the references themselves do not discuss that embryonic cells of the mouse lack PKR response. However, the skilled artisan at the time appreciated that embryonic cells of the type Wianny or Svoboda used were not PKR-proficient. The fact that Wianny and Svoboda were silent on a feature *not present* in their cells is neither surprising nor indicative that the art at the time did not have this knowledge. Further, for purposes of this appeal, the Gewirtz Declaration established that the embryonic cells of Wianny, and Svoboda were not PKR-proficient (see e.g. paragraphs 17 and 21).

The Examiner also alleges that the evidence is not convincing because neither Fire nor Appellant's claims distinguish embryonic versus developed cells, or PKR-proficiency or lack thereof. Appellant submits that the Examiner is factually incorrect. Fire, through its incorporation by reference of Montgomery and Fire, in fact, recognizes PKR-proficient cells and distinguishes cells that are not PKR-proficient.

In summary, the evidence of record, including Fire TIG, Montgomery and Fire, Wianny, Svoboda, Paddison, and Sharp (Exhibit 3, Appellant's Brief) directly addresses whether Fire enabled the ordinarily-skilled artisan, at the time of Appellant's filing, to practice Appellant's claims without undue experimentation. The Examiner has failed to adequately analyze the underlying facts as to whether Fire's disclosure enabled the practice of Appellant's invention at the time of Appellant's filing. The Examiner has instead reached her legal conclusion, that Fire was an enabling reference, by reliance on: (1) post-filing date

art, including at least one reference that the Examiner's Answer acknowledges is not available as prior art because it has been antedated (see Examiner's Answer, page 4, lines 1-7); (2) allegations that there are no differences between Appellant's claims and Fire; and (3) Dr. Fire's Nobel Prize for his contributions to RNAi.

A proper weighing of the evidence of record establishes that the ordinarily-skilled artisan, at the time of Appellant's filing, was not able to practice any methods of RNAi in mammalian, and especially human cells.

C. Impax Labs Does Not Provide the Controlling Legal Standard

The Examiner relied on *Impax Labs* for the legal standard for determining whether Fire is an enabling reference. The Examiner stated:

The Court in *Impax* clarified the legal standard for a prior art reference to be anticipatory. The Court stated “. . . anticipation does not require actual performance of suggestions in a disclosure. Rather anticipation only requires those suggestions be enabled to one of skill in the art.” The Court further stated that “[w]hether a prior art reference is enabling is a question of law based upon underlying factual findings.” The Court concluded that a ‘102 prior art reference does not have to be “effective” to be enabling and thus anticipating’ and the proper issue to consider upon deciding whether or not a prior art reference is enabling is if ‘it describes the claimed [invention] sufficiently to enable a person of ordinary skill on the art to carry out the invention.’

Examiner's Answer, p 14, lines 8-16.

Appellant respectfully submits that the Examiner has committed the same error that the Federal Circuit corrected in *Impax Labs*, i.e., a proper factual analysis was not conducted before the ultimate legal determination as to whether Fire enabled Appellant's claimed invention. In *Impax Labs*, the district court did not conduct a full factual analysis prior to making the legal determination of whether the asserted reference was enabling, but instead focused only on whether the reference provided evidence that the claimed method would be effective. *Impax Labs, Inc. v Aventis Pharms. Inc.*, 468 F.3d 1366, 1383-4, 81 U.S.P.Q.2d 1001 (Fed. Cir. 2006). The district court found that the reference contained no evidence that the method would be effective and concluded that the reference was thus, not enabling. *Id.* The Federal Circuit reversed and remanded, instructing the district court to “make the proper factual determinations and then reach its own legal conclusion” as to whether the prior art reference is enabling. *Id.*

Here, the Examiner's analysis (Examiner's Answer, page 14, line 17, through page 15, line 18.) relied on post-filing date art and the alleged a lack of "manipulative differences" between Fire and Appellant's claims, as discussed *supra* in Section B. The Examiner here was also focused on "effectiveness." The Examiner acknowledged that Fire does not provide evidence that dsRNA would be effective in cells such as mammalian cells. Noting that *Impax Labs* concluded that prior art need not teach effectiveness to be enabling, the Examiner, without conducting a proper factual analysis, concluded that Fire was enabling because it describes Appellant's claimed method "sufficiently enough to enable a person of ordinary skill in the art to carry out the invention." The Examiner erred because she did not provide adequate consideration of the factual basis for determining whether Fire is an enabling reference, as required by the court in *Impax Labs*.

Impax Labs, however, does not directly provide the standard for actual determination of whether a reference is enabling, i.e., a proper factual analysis, followed by the ultimate legal conclusion. Rather, *Impax Labs* cites *Elan* for that standard, noting that effectiveness need not be considered. *Impax Labs*, 468 F.3d at 1384. In *Elan*, the Federal Circuit reversed a summary judgment of anticipation, finding that the district court had failed to directly address the question of enablement. *Elan*, 346 F.3d at 1057. The Federal Circuit then remanded for determination of whether the reference in question enabled persons of ordinary skill in the field of the invention to practice the claimed invention *without undue experimentation, in accordance with In re Wands*. *Id.*

The legal determination of whether a prior art reference enables the practice of claims against which it is asserted thus requires a proper factual analysis, as *required* under *Elan* and *Impax Labs*. The factual analysis required by these two cases is indistinguishable because the court in *Impax Labs* cited *Elan* for the factual determination, rather than detail the required analysis therein. As *Elan* states "the factual premises of the enablement analysis for biological processes were addressed in *In Re Wands*." *Elan*, 346 F.3d at 1054-55. Here, the Examiner, like the district court in *Impax Labs*, erred in failing to undertake a proper factual analysis according to *Elan*, *Wands*, or *In re Goodman*, before making the legal determination of whether Fire enabled the practice of Appellant's claimed invention.

As set forth in full in Appellants Brief, the facts in *Goodman* are very similar to those in this appeal, particularly with respect to the statements by the patentee in a later publication regarding the practice of his generic teachings. Contrary to the statements in the Examiner's Answer (page 14, lines 1-8), Appellant has not suggested that the *legal* standard for whether

Fire enabled the practice of Appellant's claimed invention is the same as in *Goodman* or *Wands*. However, it is beyond question that the *factual analysis* of the type conducted *In re Goodman*, *In re Wands*, and *Elan* is not only applicable, but required.

Appellant set forth such an analysis of the facts of record, using the *Wands* factors in Appellant's Brief. As stated therein, proper analysis of the facts in evidence in this case shows that, at the time of Appellant's filing, the level of experimentation required to practice the claimed invention based on Fire was not only extensive, but was undue. The Examiner has concluded otherwise, based on an erroneous factual predicate that cannot stand up to proper scrutiny.

For example, the Examiner concluded that Dr. Fire's statement in FireTIG were "not evidence that Fire felt his invention was limited to invertebrate animals", but rather "his thoughts on whether this would work was (sic) mere speculation." Examiner's Answer, page 11, line 21 through page 12, line 3. The Examiner's conclusion was supported solely by citing unspecified "post-filing art." The evidentiary value of Fire TIG must be weighed retrospectively through the eyes of the skilled artisan at the time, as to what Fire enabled in his patent. Dr. Fire's comments in his later publication, like those of Dr. Goodman in his later publication in *Goodman*, were certainly strong evidence as to what Fire enabled, which clearly did not include the practice of RNAi in mammalian cells, when viewed in the light of the state of the art at the time.

In accordance with the foregoing, Appellant respectfully requests the anticipation rejection be reversed, and the claims be found to be novel and patentable over Fire. As can be seen, Fire, in combination with the knowledge in the art at the time of Appellant's filing, did not put the public in possession of Appellant's claimed methods, nor allow the ordinarily-skilled artisan to carry out the invention. Fire did not enable a person of ordinary skill in the art to practice Appellant's claimed invention without undue experimentation.

II. The References Asserted in the New Ground of Rejection Do Not Render the Claims Obvious

Appellant respectfully submits that the claims are patentable over Fire, Gewirtz, and Sharp. The rejection must be reversed because (i) the asserted combination of references does not disclose each and every element of the claimed invention; (ii) the references teach

away from the claimed invention; (iii) the references and Appellant's invention were not considered as a whole, and (iv) there could have been no reasonable expectation of success at the time, given the state of the art.

A. The Legal Standard for Obviousness Under 35 U.S.C. § 103 (a)

The legal standard for obviousness was fully briefed in Section II. A. of Appellant's Brief, and is incorporated by reference herein, as if set forth here in its entirety.

B. The New Ground of Rejection under 35 U.S.C. § 103

Claims 1, 2, 5, 7-9, 11 and 21-38 stand rejected under 35 U.S.C. § 103 (a) over Fire, Gewirtz, and Sharp. As a preliminary matter, Appellant notes that new ground of rejection presented herein is substantially similar to the ground of rejection argued in Appellant's Brief, with the exception that the Examiner has withdrawn reliance on the antedated Kreutzer reference for the new ground of rejection under 35 U.S.C. § 103(a). Appellant also notes that the new ground of rejection is nearly identical to, and largely copied verbatim from, a rejection previously overcome during the prosecution of Appellant's instant application. The Office Action mailed December 29, 2005 presented a rejection under 35 U.S.C. § 103 (a), of claims 23-27, as unpatentable over Fire in view of Gewirtz. The only substantial difference between that rejection, which was not maintained, and the current rejection, is the addition of Sharp as a general reference, allegedly providing an expectation of success (see Examiner's Answer, page 7, lines 3-5; page 9, lines 2-6). Further, claims 1, 2, 5, 7-9, 11 and 28-38 have been included in the new ground of rejection.

The new ground of rejection under 35 U.S.C. § 103 (a) set forth in the Examiner's Answer alleged it would have been *prima facie* obvious to one of ordinary skill in the art:

to substitute an dsRNA oligonucleotide in place of the antisense oligonucleotide in a method of inhibiting the expression of the oncogene c-Kit in vitro using an antisense inhibitor in human leukemia cells (as taught by Gewirtz *et al.*), wherein the dsRNA was comprised in pharmaceutical composition (as taught by Fire) because antisense inhibition of c-Kit was taught in the prior art as inhibiting the expression of KitR in human leukemia cells (as taught by Gewirtz *et al.*), because dsRNA can be used to initiate RNA interference in vitro by targeting oncogenes in human cells including leukemia (as taught. by Fire) and because relative to antisense approaches, dsRNA used to inhibit gene expression has advantages in the stability of the material to be delivered (as taught by Fire).

Examiner's Answer, page 7.

The Examiner's Answer further alleged that it would have been obvious to use a HL-60 cell line for the study of leukemia *in vitro* and further obvious to use CHP 100 to study the cellular events associated with neuroblastoma. The Examiner's Answer acknowledged that Fire does not teach the "optimal" time of incubation of said dsRNA with a cell or the "optimal" concentration of dsRNA used, but stated that it would have been obvious to one of skill in the art and "a matter routine optimization" to determine the amount of time to expose the dsRNA to achieve the most efficient interference and to determine the optimal workable ranges of a dsRNA that most efficiently caused gene interference in a cell. The rejection cited MPEP 2144.05 for the proposition that "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." Examiner's Answer, page 7-8.

The Examiner's Answer further alleged that:

[o]ne of ordinary skill in the art would have been motivated to practice a method of inhibiting the expression of the oncogene c-Kit *in vitro* in human leukemia cells or melanoma cells (as taught by Gewirtz *et al.*) using a dsRNA to initiate RNA interference wherein the dsRNA was comprised in [a] pharmaceutical composition (as taught by Fire) because antisense inhibition of c-Kit was taught in the prior art as inhibiting the expression of KitR in human leukemia cells (as taught by Gewirtz *et al.*) and because relative to antisense approaches, dsRNA used to inhibit gene expression has advantages in the stability of the material to be delivered and has advantages of sequence specificity (as taught by Fire).

Examiner's Answer, page 8.

Finally, according to the rejection:

[o]ne of ordinary skill in the art would have expected success in practicing a method of inhibiting the expression of the oncogene c-Kit *in vitro* in human leukemia cells (as taught by Gewirtz *et al.*) using a dsRNA to initiate RNA interference wherein the dsRNA was comprised in [a] pharmaceutical composition (as taught by Fire) because antisense inhibition of c-Kit was taught in the prior art as inhibiting the expression of KitR in human leukemia cells (as taught by Gewirtz *et al.*) because Fire *et al.* teach that dsRNA can be used to initiate RNA interference in human cells and because relative to antisense approaches, dsRNA used to inhibit gene expression has advantages in the stability of the material to be delivered (as taught by Fire and Kreutzer). Moreover, one would have had a reasonable expectation of success at initiating RNA interference in human cells because Sharp further supports the fact that RNAi is a general mechanism that is likely to be a general mechanism for gene regulation and may be critical for many developmental and antiviral processes.

Examiner's Answer, pages 8-9.

According to the Examiner's Answer, the invention as a whole would have thus been obvious over the asserted combination of references.

C. The Asserted References

Appellant discussed Fire, Gewirtz, and Sharp at length in Appellant's Brief (at pages 6-9, 26, and 11-12, respectively; see also discussion at section I. B., pages 6-9, *supra*). To avoid repetition, Appellant incorporates that discussion in its entirety herein by reference, as if set forth here in full.

The Examiner acknowledged that Sharp primarily discusses RNAi in invertebrates. Examiner's Answer, page 11, lines 21-22. However, it is not completely clear how Sharp is being used. In her rejection, the Examiner asserted that Sharp was merely a general reference that allegedly would provide an *expectation of success* (*id.* at page 9, lines 2-5). Responsive to Appellant's Brief, however, the Examiner asserted that language in Sharp would provide the *motivation* to reduce Fire's invention to practice in mammalian cells. *Id.* at p. 12, ln 1-3.

D. The Combination of References Does Not Render the Claims Unpatentable

For purposes of this appeal, the patentability under § 103 of independent claims 1, 22, and 28, and their respective dependent claims, will be argued separately.

1. Independent Claim 1, and Claims 2, 5, 8-9, 11, and 21 Dependent Thereon are Patentable over the Asserted References

a. The Claims

The subject matter of independent claim 1, and claims 2, 5, 8-9, 11, and 21 dependent thereon is briefed in full in Appellant's Brief, Section II.D(1)(a). That discussion is incorporated by reference herein.

b. There Would Have Been No Motivation to Combine the Asserted References

Appellant respectfully asserts that there was no motivation to combine Fire and Gewirtz.

The Examiner alleged that one of ordinary skill in the art would have been motivated to combine the Fire and Gewirtz because:

(i) antisense inhibition of c-kit was taught in the prior art as inhibiting expression of KitR in human leukemia cells (allegedly taught by Gewirtz), and

(ii) dsRNA used to inhibit gene expression has advantages in stability of the material to be delivered, and of sequence specificity (allegedly taught by Fire). (Examiner's Answer, page 8). The Examiner further alleged that Sharp teaches that RNA is a general mechanism of gene regulation that may be critical for many processes.

The Examiner is incorrect. The asserted disclosure of Gewirtz is not germane to the subject matter of claims 1, 2, 5, 8-9, 11, and 21 because those claims do not have any features directed to c-kit or antisense inhibition of KitR. The Examiner has not articulated any rational basis why the skilled artisan would be motivated to combine Gewirtz with Fire to **make the invention of claim 1**. Neither the knowledge in the art at the time of Appellant's filing, nor the disclosures of Gewirtz or Fire provide any motivation to combine. There is no basis provided, or reason given, by the Examiner as to why the references should be combined, and no particular or general motivation for the skilled artisan to do so to make the invention claimed in claim 1.

The Examiner also erred to the extent Sharp is asserted as a source of motivation to combine the references (Examiner's Answer, page 11, line 17 through page 12, line 3). The portions of Sharp referenced by the Examiner are taken out of context. Sharp, taken as whole, teaches that RNAi was **an established phenomenon in invertebrates only**, and that dsRNA-mediated suppression of specific genes **was known in plants**. Sharp concluded that it was **not known** whether any aspect of RNAi occurs in, or can be induced in, mammalian cells. In relying on Sharp, the Examiner failed to consider what the reference *as a whole* would have taught or suggested to a person of ordinary skill in the art, at the time of Appellant's filing.

The Examiner's Answer stated that Appellant's evidence of record, including Sharp, Paddison, Wianny, and Svoboda, does not *prove* that one of skill in the art would not have been motivated to practice the methods of Fire in mammalian cells. Examiner's answer page 16, line 19, through page 17, line 7. The Examiner asserted that these references actually *provide* motivation to use RNAi because Sharp states that "[p]erhaps some aspect of the RNAi effect occurs or can be induced in mammalian cells." *Id.*

Appellant respectfully asserts that the Examiner again used the wrong legal standard. Contrary to the assertion by the Examiner, it is not Appellant's burden to **prove** the negative (i.e., lack of motivation). Rather, it is the Examiner's burden to prove motivation to combine references. The Examiner must assess what the combined teachings of the references would have suggested to one of ordinary skill in the art. Where the teachings of two or more prior

art references *conflict*, the Examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit another. The Examiner here has failed to do this. The only “conflicting” teaching that the Examiner cited to counter Appellant’s evidence, and thereby support the alleged motivation to combine, is the teaching of Sharp. As Appellant has pointed out above, Sharp’s “conflicting teaching” is not conflicting, as it supports Appellant’s contention of uncertainty in the art, and thus no motivation to combine.

Finally, the Examiner must consider the state of the art **as a whole**, at the time of filing. The Examiner has also failed to do this. Instead the Examiner relied on strained readings of statements taken out of context. Further, the Examiner has not limited herself to reviewing the state of the art at the time, instead allowing post-filing art to distort the analysis. As can be seen from the evidence of record, as discussed herein, and summarized in full in Appellant’s Brief (Section I.C., pages 9-14) at the time of Appellant’s filing, the skilled artisan did not know, based on all available knowledge in the art, whether mechanisms for RNAi existed or could be leveraged for gene silencing in vertebrate, mammalian, and especially human, cells. Because the state of the art was so uncertain at the time of filing Appellant’s application, the knowledge in the art itself also did not provide any motivation to combine the Fire and Gewirtz references.

The Examiner’s Answer improperly discounted Appellant’s cited evidence, e.g., Paddison, Wianny, and Svoboda, stating that these papers merely reduced the invention of Fire to practice, thereby establishing that the art was not uncertain and not unpredictable. Examiner’s answer, page 17, lines 8-12. There is no evidence of record that states or suggests that Paddison, Wianny, or Svoboda merely reduced Fire’s invention to practice, without any contribution of their own, nor is that the case. Given its place in the biotechnological arts, and its state of relative infancy at the time of Appellant’s filing, RNAi can not reasonably be deemed “not uncertain and unpredictable” with respect to application in mammalian cells. Appellant’s evidence fairly establishes that the art was uncertain and unpredictable.

c. There Would Have Been No Expectation of Success Even if the References Were Combined

The Examiner alleged that one of skill would have had an expectation of success in practicing a method of inhibiting the expression of the oncogene c-Kit *in vitro* in human leukemia cells because:

(i) antisense inhibition of c-kit was taught in the prior art as inhibiting expression of KitR in human leukemia cells (allegedly taught by Gewirtz),

(ii) dsRNA can be used to initiate RNA interference in human cells (allegedly taught by Firer), and

(iii) dsRNA used to inhibit gene expression has advantages in stability of the material to be delivered, and of sequence specificity (allegedly taught by Fire). Examiner's Answer, page 8-9. The Examiner further alleged that Sharp teaches that RNA is a general mechanism of gene regulation that may be critical for many processes. *Id.*

As discussed above, the Examiner has taken Sharp out of context. The teachings of Sharp provide no expectation of success, because Sharp teaches that it was **not known** whether any aspect of RNAi occurs in, or can be induced in, mammalian cells. Sharp's statement of what was **not known**, or of what *might* exist, cannot provide any *expectation of success* in practicing the method of claim 1. Given the state of the art as discussed hereinabove and throughout the prosecution, there could have been no reasonable expectation of success of arriving at the claimed invention at the time of Appellant's filing.

For example, the skilled artisan at the time of Appellant's filing did not know whether mammalian systems had the required mechanisms for RNA interference. Thus, even if the skilled artisan were motivated to *experiment*, success could not be reasonably *expected* without knowing whether the mechanisms for RNAi were (i) lacking in all mammalian cells, (ii) lacking in the selected cells (e.g. embryonic vs. non-embryonic), or (iii) whether a generalized response to foreign dsRNA affecting the expression of many genes would override silencing of a specific gene. It was not known, for example, whether an RNAi effect, if it could be induced, could be induced for *a particular gene*, or whether only *certain genes* might be susceptible to silencing by RNAi. Further the teachings of Fire itself, through its incorporation by reference of Montgomery and Fire, negate any reasonable expectation of success by raising doubt as to what impact the PKR response would have in any PKR-proficient mammalian cell. There was, therefore, no basis for the skilled artisan to *reasonably* expect success at the time of Appellant's filing, from the combined disclosures of Fire and Gewirtz.

Appellant's specification showed that PKR and other cellular response mechanisms could be overcome, even when using long dsRNA. This was contrary to the prevailing wisdom in the art. The PKR response was considered particularly relevant to long dsRNA in mammalian cells. Only after Appellant's disclosure and later work, when it was known that mammalian cells were susceptible to RNAi-induced gene-specific silencing, could there have been any **reasonable** expectation of success. Prior to Appellant's invention, the art lacked adequate information to allow the skilled artisan to interpret experiments, or adjust conditions to reasonably expect, or generate, a successful result.

The Examiner's Answer also stated that an expectation of success would derive from Gewirtz's teaching of methods of silencing gene expression using antisense RNA in human leukemia cells, and because Fire taught that dsRNA can be used, and had advantages in stability. These two observations could not, at the time of Appellant's filing, provide any reasonable expectation of success in practicing Appellant's claimed methods because there was insufficient knowledge in the art to put the two observations together. Antisense technology was still quite unpredictable and uncertain, and RNAi was not yet known to occur in mammalian cells.

d. The Asserted References Do Not Disclose Every Feature of the Claims

The asserted references, even in combination, do not disclose each and every feature of the claims. Fire has been discussed, *supra*. Gewirtz is related to antisense technology and discloses nothing related to RNAi, and nothing particularly related to the invention of claim 1. No claim dependent on claim 1 is currently directed to c-kit sequences described in Gewirtz.

The Examiner's rejection alleged that Fire teaches a method for inhibiting expression of a target gene using double-stranded RNA in a cell *in vitro* wherein the cell is from an animal (citing Fire, claims 1 and 6), and the dsRNA has a length less than about 830 bp (citing Table 1). The rejection also alleged that Fire teaches that the cell with the target gene may be derived from or be contained in any organism (column 8, lines 13-14) and that examples of vertebrate animals include mammals and human (column 8, lines 35-37) and that the cell having the target gene may be "immortalized or transformed, or the like" (column 8, lines 52-55). The rejection further alleged that Fire states that "the present invention could be used for treatment or development of treatments for cancer of any type, including solid tumors, sarcomas, and leukemias. . ." (quoting column 10, lines 26-28).

The Examiner's Answer asserted that "the limitation 'selecting a human cell expressing the target gene' is **not defined** in the specification, so for prior art purposes, this recitation is being interpreted to mean a cell line that contains a target gene and is capable of being treating [sic] with a dsRNA...". The rejection alleged that Fire teaches target genes that are oncogenes in column 11, and that lipid-mediated carrier transport can be used to introduce nucleic acids to cells (citing column 9, lines 55-60 of Fire). The rejection also stated that Fire teaches that inhibition of gene expression refers to the absence (or observable decrease) in the level of protein and/or mRNA product from a target gene as determined by measurement of the target gene or expression from said target gene. Further, it is alleged (citing column 5, lines 30-37 of Fire), that Fire teaches that gene disruptions created with the methods disclosed therein, may be used to discover the function of a target gene and to produce disease models in which the target gene is involved in causing or preventing a pathological condition. Fire, according to the rejection, also discloses that relative to antisense approaches, dsRNA has advantages in the stability of the material to be delivered (citing Fire at column 3, line 20).

Contrary to the statements in the Examiner's Answer, each and every step of Appellant's claimed method is not provided in the asserted references. Appellant's claimed method expressly provides a method for disrupting expression of a mammalian target gene at the mRNA level **in a human cell**, wherein the method comprises initiating RNA interference (RNAi) *in vitro* by exposing **the human cell** to a double-stranded RNA (dsRNA) homologous to the target gene, wherein the dsRNA consists essentially of two complementary linearized strands of RNA, the transcription of each is independently controlled to generate paired RNAs of defined length.

The Examiner erred as a matter of law in not giving weight to the express claim element requiring "**disrupting expression . . . in a human cell**", and "**exposing the human cell to dsRNA**." No authority requires Appellant to provide a definition of a claim element to be accorded weight during examination. The element is understood by the plain meaning of the words "**in a human cell**." The Examiner must give full weight to this feature and may not disregard the claimed feature or substitute a definition such as "a cell that contains a target gene and is capable of being treated with a dsRNA." The invention, i.e., the claim with all its elements, must be considered as a whole. Here, the claim expressly includes the feature "**human cell**", which is readily understandable to the skilled artisan by its plain meaning.

Further, claim 1 requires “initiating RNAi in the human cell.” Fire did not disclose, nor would the ordinarily skilled artisan be able to practice, “initiating RNAi in a human cell” or initiating RNAi in **any** mammalian cell at the time of Appellant’s filing. This is evidenced by the state of the art as shown in the record and described above, e.g., as admitted by Dr. Fire and further shown by the other evidence spanning the time from Fire’s filing through Appellant’s filing.

As discussed above in response to the Examiner’s Answer with respect to the anticipation rejection, Appellant respectfully submits that Fire did not enable the skilled artisan to carry out Appellant’s claimed invention without undue experimentation, or to carry out the practice of any methods of initiating RNAi in any vertebrate cells. Accordingly, Fire did not disclose the claimed methods of *initiating RNAi in human cells*, since it did not enable those methods to be carried out. The skilled artisan having the Fire reference before him did not know how to initiate RNAi in an mammalian cell. Since Fire did not enable the practice of Appellant’s claimed invention, and neither Gewirtz nor the general knowledge in the art cured this deficiency, the combination of Fire and Gewirtz does not render the claimed invention obvious. Appellant respectfully submits that the Examiner did not establish a *prima facie* case with respect to claims 1 and claims 2, 5, 8-9, 11, and 21 dependent thereon.

e. The Prior Art Teaches Away From the Claimed Invention

The evidence of record shows that the state of the art, at the time of Appellant’s filing, was fraught with uncertainty and unpredictability with respect to the application of RNAi in mammalian systems. The art teaches away from the invention of Appellant’s claim 1.

As discussed previously *supra*, and in Appellant’s Brief, Fire TIG admitted that “the simple protocols used for invertebrate and plant systems are unlikely to be effective [in vertebrates].” Also as discussed therein, Montgomery and Fire did not answer their own question as to whether RNA-interference mechanisms have counterparts outside of plants and nematodes. Montgomery and Fire concluded that any gene-specific interference by dsRNA in PKR-proficient mammalian cells would require “a transient lapse in the PKR response”, or an amount of dsRNA that was “incapable of activating PKR”. As discussed above, Sharp concluded that perhaps “some aspect of the RNAi effect occurs or can be induced in mammalian cells.” After Appellant’s filing date, the Kreutzer Patent Application stated that despite successes in the invertebrates and plants, “until recently the general perception in the art has been that RNAi cannot be made to work in mammals.” The Kreutzer Patent

Application further stated that the prevailing belief was that “protocols used for invertebrate and plant systems would not be effective in mammals due to the interferon response, which leads to an overall block to translation and the onset of apoptosis.” Finally, in 2002, also after Appellant’s filing date, Paddison professed that the *first* indication that the RNAi response **might** extend to mammals came from the observation that injection of dsRNA into early mouse embryos induced sequence-specific silencing.

Because at least up until the filing of Appellant’s application, the art questioned the very existence of RNAi mechanism in mammalian systems, the skilled artisan would not have looked to develop methods for practicing RNAi in mammalian cells. Skilled artisans were looking to other methods at the time. For example, as described in Fire, antisense inhibition was the most common approach during that time and substantial research effort was focused there, as well as on triple helix or co-suppression approaches. (see e.g., Fire, Background of the Invention). The art as a whole, including Fire, taught away from the invention of claim 1.

Contrary to the statements in the Examiner’s Answer (e.g. on page 18, lines 9-16), Fire teaches away from Appellant’s claimed invention, at least because Montgomery and Fire is incorporated by reference therein, and thus constitutes a teaching of Fire as if set forth therein.

2. Independent Claim 22, and Claims 23-27 Dependent Thereon are Patentable Over the Asserted References

a. The Claims

The subject matter of independent claim 22, and claims 23-27 dependent thereon is briefed in full in Appellant’s Brief, Section *II.D(3)(a)*. That discussion is incorporated by reference herein.

b. There Would Have Been No Motivation to Combine Fire and Gewirtz

There would have been no motivation to combine Fire and Gewirtz. The motivation alleged in the rejection is as stated above:

(i) antisense inhibition of c-kit was taught in the prior art as inhibiting expression of KitR in human leukemia cells (allegedly taught by Gewirtz), and

(ii) dsRNA used to inhibit gene expression has advantages in stability of the material to be delivered, and of sequence specificity (allegedly taught by Fire). Sharp allegedly

teaches that RNA is a general mechanism of gene regulation that may be critical for many processes.

Although Fire taught that double-stranded RNA is more stable than single-stranded RNA used in antisense approaches, that teaching must be considered within the context of the state of the art. As discussed above in detail, at the time of Appellant's filing, the art as a whole had substantial doubts about RNA interference in mammalian cells. It was not known whether mechanisms for RNAi existed, or whether gene-specific interference could be induced in mammalian systems. It **was known** was that post-embryonic mammalian cells had overarching and generalized responses to external dsRNA, especially long dsRNA, that had evolved to limit the impact of foreign RNA, such as long viral dsRNA, in the cell. It **was known** in the art at the time of Appellant's filing that these generalized responses to dsRNA could lead to cell death to prevent expression of foreign RNA in a mammalian system, particularly for long dsRNA. It **was not** known how to overcome these defensive responses to external dsRNA, or if they could be overcome.

While Gewirtz provides the c-kit sequences, Gewirtz could not provide any motivation to resolve the issues in Fire regarding RNAi in mammalian systems. Gewirtz was solely focused on antisense technology in human cells. Accordingly, a skilled artisan at the time would not have been motivated by the combined teachings of Fire and Gewirtz, nor by any knowledge in the art at the time, to make Appellant's claimed invention. The teachings of the two references were insufficient to motivate the asserted combination. Further, there was no knowledge in the art that could bridge the gap in the skilled artisan's knowledge. Sharp is alleged to provide a general motivation, but considering Sharp *as a whole*, it does not provide the missing information required by the skilled artisan to actually undertake the combination, and actually leads away from the asserted combination as it created yet more doubt as whether any such combination would be useful or successful.

Accordingly, there was no motivation for the skilled artisan to combine Fire and Gewirtz to arrive at the invention of claim 22, or claims dependent thereon, as no motivation was provided in the references themselves, nor in the art as a whole.

c. There Would Have Been No Expectation of Success; The Art Teaches Away From the Claimed Invention.

The relevant arguments concerning these factors have been set forth above for claim 1 and claims dependent thereon. Each is therefore incorporated by reference herein as an

alternative ground for reversing the rejection. Thus, even if the asserted references were combined, there would have no reasonable expectation of success in practicing the invention of independent claim 22 or dependent claims 23-27. Further, the art as whole, including Fire, teaches away from those claims, as it cast doubt on whether the mechanisms for RNAi would function for gene-specific silencing in mammalian cells, and whether the mechanisms even existed.

d. The Asserted References Do Not Disclose Every Element of the Claims

As to claims 22-27, contrary to the assertions in the Examiner's Answer, each and every step of the claimed methods are not provided in the cited references alone or in combination. Claim 22 expressly provides a method for **disrupting expression of a mammalian target gene *in vitro in a human cell***. The claimed method comprises providing an RNA sequence homologous to a portion of the target gene, **wherein the RNA is capable of inducing RNAi of the target gene**.

Fire did not enable Appellant's invention for gene-specific silencing in vertebrate cells because the skilled artisan could not carry out those methods, as has been discussed fully above. The Examiner erred in giving no weight to the expressly claimed feature requiring **disrupting expression . . . *in a human cell***, and **exposing the human cell**. This claim element is understood by the plain meaning of the words "*in a human cell*," for which no definition or further explanation is required. The Examiner **must** give full weight to the express language of the claim, and **may not** substitute a definition such as "a cell that contains a target gene and is capable of being treated with a dsRNA." Claim 22, with all its express elements and features, must be considered as a whole. Here, claim 22, as well as the dependent claims 23-27, expressly include language directed to human cells, which by its ordinary meaning is readily understandable to the skilled artisan.

Claim 22 also requires that the provided RNA be ***capable of inducing RNAi of the target gene***. Fire did not teach, or enable, the ordinarily skilled artisan to practice Appellant's claimed method. The characteristics of an ***RNA capable of inducing RNAi of a target gene*** in mammalian cells were not known prior to Appellant's filing date. This is evidenced by the state of the art, as shown in the record. As discussed above with respect to the rejection of claim 1 for obviousness, Fire did not enable the skilled artisan to carry out Appellant's claimed invention. The practice of methods involving RNAi in vertebrate cells was not in the public's possession. Accordingly, Fire did not **teach** Appellant's claimed

methods *in human cells*, since it did not enable the methods to be carried out in human cells and did not teach any RNAs that were capable, at the time, of inducing RNAi in human cells. Gewirtz teaches treatment of human cells with antisense c-kit RNA, however Gewirtz teaches nothing about RNAi in human cells or in any cells. Fire, alone or in combination with Gewirtz, did not teach any RNA capable of inducing RNAi in a human cell. Gewirtz did not at the time provide the information lacking in Fire needed to practice the claimed invention. The asserted combination does not result in the invention of Appellant's claim 22. The skilled artisan having Fire and Gewirtz before him could not have carried out a method for disrupting expression of a mammalian target gene *in vitro in a human cell* comprising providing an RNA sequence homologous to a portion of the target gene, wherein the *RNA is capable of inducing RNAi of the target gene*. Appellant respectfully submits that the Examiner has not made out a *prima facie* case of obviousness with respect to claims 22-27.

3. Independent Claim 28, and Claims 7 and 29-38 Dependent Thereon, are Patentable Over the Asserted References

Independent claim 28, and claims 7 and 29-38 dependent thereon, currently stand rejected as unpatentable over the asserted references under §103, but have been deemed to be novel by the Examiner.

a. The Claims

The subject matter of independent claim 28, and claims 7, and 29-38 dependent thereon is briefed in full in Appellant's Brief, Section *II.D(4)(a)*. That discussion is incorporated by reference herein.

b. There is No Motivation to Combine the References; There Would Have Been No Expectation of Success; and Fire and the Art as a Whole Teach Away From the Claimed Invention

As set forth above for claim 1, and claims 22-27, there would have been no motivation to combine the references, there was no reasonable expectation of success, and the skilled artisan would have been led in other directions because the art taught away from Appellant's claim 28. In particular, there is no motivation found in Fire, Gewirtz, or the knowledge in the art at the time, to combine Fire and Gewirtz. There was no basis on which the skilled artisan could have formed a *reasonable* expectation of *success* in arriving at

Appellant's claim 28 or claims dependent thereon. The art-recognized doubts are well-documented, including in Montgomery and Fire, which is incorporated by reference into, and thus is part of, Fire itself. Gewirtz adds nothing to provide the skilled artisan with a reasonable expectation of success in practicing methods of RNAi. Finally, the art, including Fire, taught away from the claimed invention because of the doubts expressed by skilled artisans that RNAi could be used for gene-specific silencing in mammalian cells, especially using the simple protocols used in invertebrate systems.

c. The Asserted References Do Not Disclose Every Limitation of the Claims

The asserted references, alone or in combination, do not disclose each and every element of Appellant's invention set forth in claim 28 and claims dependent thereon. The claims are thus not *prima facie* obvious. Claim 28 is directed to methods for disrupting expression of a target gene *in a human cell*. Each express claim element must be given its due weight. Here, the claim element is understood by the skilled artisan based on the plain meaning of the words used. No definition is required.

Claim 28 also requires the steps of *selecting a human cell expressing the target gene*; preparing a double-stranded RNA (dsRNA) consisting essentially of a first strand homologous to the target gene, and a second strand complementary to the first strand; *exposing the human cell to the dsRNA* in a reaction mixture *in vitro*, *under conditions permitting the dsRNA to enter the cell*; and *incubating* the reaction mixture *for a time sufficient to allow the initiation of RNA interference*, thereby disrupting the expression of the target gene.

Appellant respectfully submits that the Examiner erred in not giving due weight to the express requirement for a human cell. In addition, Appellant further submits the Examiner erred in concluding that the steps of *exposing the human cell to the dsRNA* in a reaction mixture *in vitro*, *under conditions permitting the dsRNA to enter the cell*, and *incubating* the reaction mixture *for a time sufficient to allow the initiation of RNA interference*, are mere optimization steps.

The teachings of the asserted references alone or in combination did not enable the practice of the claimed methods in human cells at the time of Appellant's filing. This has been discussed above fully and such discussions are incorporated by reference herein.

Appellant also respectfully notes that to the extent the rejection is premised on MPEP 2144.05, it is incorrect as a matter of law. MPEP 2144.05 provides in relevant part :

Generally, differences in concentration or temperature will not support the patentability of subject matter *encompassed* by the prior art *unless* there is evidence indicating such concentration or temperature is critical.

The subject matter of claim 28 is not *encompassed* by the asserted prior art. The Examiner's Answer acknowledges that Fires does not teach an optimal time of incubation, or an optimal concentration of dsRNA. More significantly, however, Fire does not teach any time of incubation for exposing a human cell to dsRNA, or any concentrations of dsRNA to use for initiating RNAi in human cells.

A *prima facie* case of obviousness *may* be made when the *only* difference from the prior art is a difference in the range or value of a particular variable. *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003); *In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990) (emphasis added). As *In re Peterson* makes clear, an obviousness rejection under MPEP 2144.05 is, therefore, available when the *only* difference between the claimed invention and the prior art is a difference in range or value of a particular variable. Here, the combination of Fire and Gewirtz does not encompass the subject matter of claim 28 or any claim dependent thereon. The prior art failed to teach the whole genus of methods because the asserted prior art does not teach any methods that are enabled in human cells. Fire, alone or in combination with Gewirtz, does not disclose any range or value regarding conditions for exposing the human cells to dsRNA to allow uptake of the dsRNA, or any range or value regarding times for incubating the reaction mixture to allow initiating RNA interference. In short, the asserted prior art does not teach the conditions of Appellant's claimed methods. Accordingly, the Examiner has failed to present a *prima facie* case of obviousness with respect to claim 28, and claims dependent thereon.

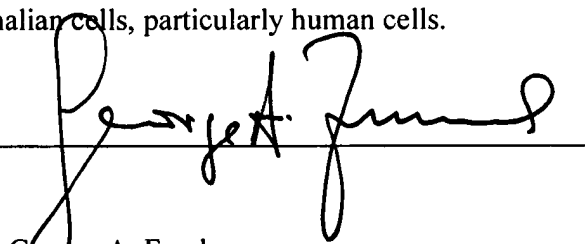
Further, even if the claimed conditions and times were somehow found to be "encompassed" by the asserted prior art, Appellant has shown that the conditions were critical to the success of the claimed invention. As shown in the working examples, insufficient incubation time resulted in the absence of gene silencing. The working examples also showed that the RNAi response was dose-dependent. If the concentration of dsRNA was too low, no response was seen. However, if the dose of dsRNA was too high, it was toxic to the exposed cells. Accordingly, to the extent the rejection is premised on MPEP 2144.05, it is improper, because the subject matter of claim 28 is not encompassed by the prior art, and the conditions can determine the success of the claimed invention.

III. Conclusion

Appellant's claims 1, 2, 5, 7-9, 11, 21-22, and 24-27 are novel over Fire and the rejection for anticipation by Fire should be reversed. The rejection relies on "vague and general language" in Fire that did not, at the time of Appellant's filing, enable the practice of Appellant's claimed invention. Further, the Examiner applied an improper legal standard for determining whether Fire enabled the practice of Appellant's claims because a proper factual analysis was not conducted, and the Examiner relied instead on post-filing date art and a lack of manipulative or structural differences.

The rejection for obviousness in view of Fire, Gewirtz, and Sharp should also be reversed. The Examiner failed to make a *prima facie* case of obviousness based on the asserted references. The combination of Fire and Gewirtz, would not have resulted in the claimed invention of any of independent claims 1, 22, or 28, or any claim dependent thereon. Further, the state of the art was such that there could not have been any reasonable expectation of success. The evidence of record establishes that the art lacked sufficient information to carry out the claimed methods with any expectation of success. Finally, the references themselves and the art as a whole taught away from the methods of claims 1, 22, and 28. It was widely believed, including by Dr. Fire, that RNAi mechanisms did not exist, or were not exploitable for gene-specific silencing in mammalian systems. Further, the asserted references do not teach or enable an ordinarily skilled artisan to carry out the methods claimed in claims 28-38 and claim 7 because they do not provide the critical conditions needed to practice the methods in mammalian cells, particularly human cells.

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